

## REMARKS

Applicant wishes to thank Examiner Allen for the helpful telephone interview conducted May 24, 2004, during which the claim amendments presented herein were discussed in view of the outstanding rejections, and during which she agreed to consider their entry to overcome such rejections. In particular, modifications to the preamble and outcome of the independent claims were discussed, and Applicants agreed to amend the claims to recite that a sequence is "present" in a said database if it contains 20 consecutive nucleotides of sequence identical to a sequence in said database.

Claims 1-26, 29-31, 50, 51, 53-58 and 60-64 are pending. Claims 1-8, 21, 23, 50 and 58 are amended herein. Claim 50 is amended to recite that the "plurality of expressed sequences is from a human host organism" in part to further distinguish the scope of claim 50 as amended from that of claim 3 as amended. Claim 53 is cancelled herein, and claim 54 is amended to reflect the change in dependency required by cancellation of claim 53. The amendments add no new matter.

### Rejections under 35 U.S.C. §112, First Paragraph:

Independent claims 1-3 and 50 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Final Office Action states:

Independent claims 1, 2, 3, and 50 have been amended to be directed to methods of using a computer system to determine the presence of a microbe inhabiting a host organism. The final step in each claim recites "wherein absence... indicates that said at least one sequence is a candidate sequence belonging to a microbe, thereby indicating the presence of a microbe inhabiting said host organism." The method steps as recited still do not provide the information required by the goal of the preamble. The methods as written do not evaluate the candidate sequence to determine if in fact they correspond to a microbial sequence. The steps as written are more properly a method of identifying candidate microbial sequences. Presently, the steps only indicate that at least one sequence is not present in the database of the host organism genomic sequences.

Applicants respectfully disagree.

Applicant submits that the proposed amendments to independent claims 1-3 and 50 are sufficient to overcome this rejection. Specifically, Applicant submits that the preamble of each of these claims is proposed to be amended to recite “A method of using a computer system to evaluate nucleic acid sequences of a non-microbial host organism for the presence of a candidate microbial sequence indicative of the presence of a microbe in a host organism.” The outcome of each of these claims has also been amended to agree with this preamble, e.g., claim 1 recites “wherein the absence of said candidate microbial sequence in said database is indicative of the presence of a microbe in said host organism,” claim 2 recites “wherein the absence of said sequence indicates that said sequence is a candidate microbe sequence, which is indicative of the presence of a microbe in said host organism,” claim 3 recites “wherein the absence of at least one of said expressed sequences in said database indicates that said at least one sequence is a candidate sequence belonging to a microbe, which is indicative of the presence of a microbe in said host organism,” claim 50 recites “wherein the presence of said candidate microbial sequence is indicative of the presence of a microbe in said host organism.”

The Final Office Action also states, that

“Likewise, the method steps of claim 58 do not determine the presence of a microbe inhabiting host organism as required by the preamble. The steps only identify the presence of an expressed sequence in common with at least one non-microbial host organism. This would include, for example, repeat elements.

Applicant respectfully disagrees.

Applicant submits that claim 58 as proposed to be amended has the same modification to the preamble as proposed for claims 1-3 and 50, i.e., “a method of using a computer system to evaluate nucleic acid sequences of a non-microbial host organism for the presence of a candidate microbial sequence indicative of the presence of a microbe in a host organism.” Similar to claims 1-3 and 50, claim 58 is also proposed herein to be amended to recite “wherein the presence of said candidate microbial sequence in said database is indicative of the presence of a microbe in said host organism.” Thus, Applicant submits that the preamble and outcome are in agreement, and the proposed amendments obviate this ground of rejection. With regard to repeat elements, Applicant

also notes that claim 58 is specifically drawn to the use of “expressed sequence information.” However, repeat elements are not generally expressed, so the claim should not be affected by any potential similarities between repeat elements.

In view of the above, Applicant submits that the proposed amendments obviate this ground of enablement rejection of claims 1-3, 50 and 58, as well as the rejection of claims dependent from them as it relates to this ground of rejection.

The Final Office Action also states:

The only claim that comes close to addressing this problem {i.e., the problem regarding the disagreement between preamble and outcome} is claim 23. However, the step set forth here requires no result (e.g. use candidate sequence as query sequence and determine if candidate sequence is present or absent) and even if it did, would generate a result which is not used in the step determining presence or absence of the independent methods (e.g. absence of the candidate sequence in the microbial database means the candidate sequence is not microbial).

Applicant submits that the proposed amendment to claim 23 is sufficient to overcome this rejection. Specifically, the claim is proposed to be amended to recite the active step of “using said candidate sequence as a query sequence to search a database of microbial sequences,” and the outcome of the claim is spelled out as “wherein the presence of said candidate sequence in said database of microbial sequences identifies said candidate sequence as a microbial sequence.” Support for the proposed amendment language is provided at page 5, lines 10-11.

The Final Office Action also maintains the prior enablement rejection relating to the terms “presence” and “absence” and how they are determined. The Office Action states

“As set forth in the prior Office action the claims have no limitations as to how presence or absence of a sequence is determined. Applicant has argued that the claim recitations of presence or absence are limited by the specification’s matching definition. Applicant points to page 8 and relies upon the definitions of “match,” “present,” and “absent.” The specification recites that a match between sequences is considered to be “a level of sequence similarity equivalent to a BLAST score ranging from 40 (equivalent of 20 consecutive identical nucleotides) to 2000 (the equivalent of 1000 consecutive identical nucleotides).” This does not limit

the claims to a match of 20 consecutive or 1000 consecutive identical nucleotides for determining presence or absence. It cannot be determined from the specification what degree of similarity with different runs of consecutive identical nucleotides would give a BLAST score ranging from 40-2000 nor what particular version of BLAST nor the parameters/penalties applicant intends for determining such scores.

Applicant respectfully disagrees.

Applicant submits that the proposed amendment to claims 1-3, 50 and 58 to recite “wherein a sequence is present in said database if it contains 20 consecutive nucleotides of sequence identical to a sequence in said database” is sufficient to overcome this ground of rejection. The amendment is supported in the specification at page 8, lines 18-20, i.e., the passage cited in the Final Office Action which recites the definition of a “match” between sequences as including “the equivalent of 20 consecutive nucleotides” to “the equivalent of 1000 consecutive equivalent nucleotides” as judged by a BLAST alignment. This definition is supplemented on the same page of the specification by the definition of “present” at lines 21-22, which states that a sequence is “present” in a database if the database contains a sequence that matches the query sequence. Applicant submits that where the “presence” of a sequence is defined in the manner of the proposed amendment, it is not necessary to recite within the claim what is meant by “absence” or “absent.” That is, it is clear that a sequence that is not “present,” as the claim recites, is “absent.” Applicant respectfully requests withdrawal of this ground of rejection.

The Final Office Action also maintains the enablement rejection based upon perceived problems with potential database contamination. Specifically, the Final Office Action states

As set forth in the prior Office action, the specification does not provide databases containing expressed sequence tags (ESTs) or genomic sequences for all host organisms embraced by the claims. While the specification indicates that many such databases are available, there is no evidence that these databases possess the type of sequence integrity (produced from host organisms not having a particular pathogenic condition, see for example claim 8) required by the claims. Applicant argues that databases containing contaminating microbial sequences can be used successfully in the methods and proffers the Meyerson declaration in support thereof. This is not persuasive. The claims require databases

containing or excluding particular types of sequence data. To enable the claimed methods, these databases must be enabled. Applicant is arguing that a different method using a different type of database is enabled.

Applicant's response is viewed as an admission that databases such as those set forth in claims 2, 3, 8, for example, would not have been available at the time of the invention.

Applicant respectfully disagrees.

Applicant submits that, using databases available at the time of filing, Applicant has successfully tested the claimed methods, as described in the Examples and in the Rule 132 Declaration filed July 10, 2003. Thus, the specification describes databases available at the time of the invention that are not contaminated in a way that precludes the function of the claimed methods. Further, Applicant notes that the potential for microbial contamination of the databases is irrelevant because one is looking for sequences that are not present in the database. That is, only if a sequence is not present in the database is it identified as a candidate microbial sequence, meaning that if a microbial sequence is present in the database, it will not be reported as absent from the database.

While the possibility for microbial contamination of the database is generally not relevant to the functioning of the claimed methods, Applicant has proposed amendments herein that remove any lingering doubt. Specifically, claim 2 is proposed to be amended to remove the language "which do not harbor the microbe," and claim 8 is amended to remove language regarding a database of sequences from "host organisms not having said pathogenic condition." In view of the proposed amendments, and the demonstration that the claimed methods work with databases available at the time of filing, Applicant respectfully requests withdrawal of this ground of rejection.

In view of the above, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, Second Paragraph:

Claims 4-6 are rejected under 35 U.S.C. §112, second paragraph because "these appear to be circular claims requiring knowing what one would find BEFORE the method is executed." Applicant respectfully disagrees.

Applicant proposes herein to amend claim 4 to recite the active step of “comparing said candidate sequence to a database of microbial sequences,” and reciting the outcome of the claim “wherein the presence of a said candidate sequence in said database of microbial sequences identifies said candidate sequence as belonging to a symbiotic microbial organism.” That is, if a candidate sequence is present in a microbial sequence database, the identity of the microbe bearing that sequence will be known, and it will also be known whether or not the microbe that comprises that sequence is a symbiotic microbial organism. As noted above, the proposed amendment language is supported on page 5, lines 10-11, and also at page 3, lines 3 and 4.

Claim 5 is dependent from claim 4, and the proposed amendment to claim 4 aids in correcting any similar problem with regard to claim 5. Further amendment to claim 5 is proposed in order to further clarify that the identification of the microbe as a symbiotic microbe as described in claim 4 can further identify the candidate sequence as belonging to a mutualistic, commensal or parasitic organism (see specification page 3, lines 3 and 4). The proposed amendment to claim 6 is similar to the amendment proposed for claim 4. Applicant submits that the proposed amendments are sufficient to overcome the grounds of rejection of claims 4-6 under §112, second paragraph.

Claim 21 is rejected under §112, second paragraph because it recites the identification of candidate sequence through subtractive hybridization. The Office Action states that this is confusing because claims 3 and 10, from which claim 21 depends, identify the candidate sequence by computationally searching databases.

Applicant submits that the specification describes methods in which, before computational analysis, the sequences from the host organism suspected of harboring a microbe are enriched for sequences present in the host organism which are not present in a plurality of host organisms which do not harbor a microbe (see page 3, lines 14-19). In these instances, the enrichment step will be performed using a subtractive hybridization method (i.e., an actual or “wet” experimental method), and the resulting sequences, enriched for the presence of sequences not present in the plurality of other host organisms, are then fed into the computational methods as claimed in the broader claims.

In order to clarify the claim, Applicant has proposed herein an amendment in which clause (a) of the claim recites “wherein said sequence information from a plurality of expressed sequences,” e.g., sequences later used to search a database, “comprises sequences identified using a subtractive hybridization method.” Applicant submits that the proposed amendment is sufficient to overcome this §112, 2<sup>nd</sup> paragraph rejection of claim 21.

Claims 23 and 24 are rejected as “confusing because the added step doesn’t make clear if or how the results of any query are used in determining the presence of a microbe inhabiting a host organism.” Applicant proposes herein to amend claim 23 to recite the active step of “using said candidate sequence as a query sequence to search a database of microbial sequences,” and to specify that “the presence of said candidate sequence in said database of microbial sequences identifies said candidate sequence as a microbial sequence.” Applicant submits that the claim as proposed to be amended makes it clear that the presence of a candidate (query) sequence in the microbial database identifies the candidate sequence as a microbial sequence. Applicant submits that the proposed amendment is sufficient to overcome this §112, 2<sup>nd</sup> paragraph rejection of claim 23. Further, because claim 24 is dependent from claim 23, the proposed amendment to claim 23 is sufficient to overcome the rejection of claim 24.

The Office Action states that claim 53 is confusing in depending upon cancelled claim 52. Applicant proposes herein to amend the dependency of claim 52 to depend only from claim 51, which amendment is sufficient to overcome this ground of rejection.

In view of the above, Applicant respectfully requests withdrawal of the §112, 2<sup>nd</sup> paragraph rejections of claims 4-6, 21, 23, 24 and 53.

Rejections under 35 U.S.C. §102:

The rejection of claims 1, 3-6, 50, 51, 53, 58 and 59 under 35 U.S.C. §102(b) over Sabatini et al. was maintained in the Office Action. The Office Action states:

“Sabatini et al. determines presence or absence of sequences thereby identifying candidate sequences as required by the claims. One of

ordinary skill in the art would have reasonably concluded if the host sequence searched wasn't found in the host organism sequence database, it was a candidate sequence as belonging to another organism, including microbes."

Applicant respectfully disagrees.

Applicant submits that Sabatini et al. differs from the claimed methods in at least the following ways. First, Sabatini et al. does not teach the comparison of sequence information from a host organism of a given species to a database of sequence information from the same host organism species. Sabatini et al. instead refers repeatedly to the comparison of genomic sequence data from "different organism types" (see, e.g., column 2, lines 13-15, and 32-65).

Second, Sabatini et al. does not teach a method wherein a sequence is present in a database if it contains 20 consecutive nucleotides of sequence identical to a sequence in the database," as required by the claims.

Third, nowhere does Sabatini et al. teach that the absence of at least one sequence in the database indicates that the at least one sequence is a candidate microbial sequence, or that the presence of the candidate microbial sequence is indicative of the presence of a microbe in the host organism, as required by the claims.

Because the reference does not teach all elements of the claimed invention, Applicant submits that Sabatini et al. cannot anticipate the claimed invention. In view of this, Applicant respectfully requests the withdrawal of this rejection under §102(b).

In view of the above, Applicant submits that all issues raised in the Final Office Action have been addressed herein. Applicant respectfully requests entry of the proposed amendments and reconsideration of the claims.

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Respectfully submitted,

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